

Application No. 10/050,000
Amendment dated August 9, 2007
Reply to Office Action of February 9, 2007

Docket No.: 0365-0529P

REMARKS

Enclosed herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a Substitute Sequence Listing to be inserted into the specification as indicated above. The Substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a disk copy of the Substitute Sequence Listing. The disk copy of the Substitute Sequence Listing, file "2007-08-06 0365-0529P.ST25", is identical to the paper copy, except that it lacks formatting. In no way do the paper copy nor the disk copy of the Substitute Sequence Listing introduce new matter into the application.

The Sequence Listing is amended to include the sequence disclosed on page 13, line 13 of the specification as noted in the Office Action. The Sequence Listing is also amended to identify the present application by filing date and serial number and to correct matters of form. No new matter is introduced by these amendments.

Issues regarding Objections within the Specification

The disclosure is objected to because of the following informalities: In the specification on page 1, lines 6, 7 and 10 applicants have referred to the preamble of claims 1, 12 and 34, respectively. Applicants amended the specification to remove such language and rewrote the stated phrase that is in the preamble. This should eliminate confusion should a particular claim be canceled.

Additionally, the present application contains sequence disclosures at page 13, line 13 that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with one or more of the requirements of 37 C.F.R. § 1.821 through 1.825. Applicants have amended the specification to be in compliance with the Sequence Rules.

Status of the claims

Claims 1-3 and 5-34 are currently pending in the present application. The Office Action is non-final. Claims 10-31 are withdrawn from consideration. Claims 1-3, 5-9 and 32-34 remain pending in the present application. Claim 1 has been amended as set forth herein. Claims 2-3 and 14-31 have been cancelled herein. All amendments and cancellations are made without prejudice or disclaimer. New claims 35-42 have been entered herein. No new matter has been added by way of the present amendments. Specifically, the amendments to Claim 1 are supported by the specification at, for instance, at page 16, lines 24-26 and page 18, lines 11 to 24. Support for newly added claim 35 and 36 can be found in the present specification at page 16, lines 24-26. Support for newly added claim 37 can be found in the present specification at page 18, lines 11-24. Support for newly added claim 38 can be found in the present specification at page 18, lines 11-24 and Example 2 at page 20, lines 25-31. Support for newly added claims 39 and 40 can be found in the present specification at page 11, lines 5-7, page 16, lines 24-26, page 18, lines 11-24 and Example 2 at page 20, lines 25-31. Support for newly added Claim 41

can be found on page 16 lines 24-26. Support for newly added Claim 42 can be found at page 24, line 22, Example 6.

Applicants respectfully request reconsideration of each of the pending claims (i.e., Claims 1-3, 5-9 and 32-34), including the amended and new claims based on the following comments.

Issues Under 35 U.S.C. § 112, First Paragraph

Enablement

Claims 1-2, 5-9 and 32-34 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. (*See*, Office Action of February 9, 2007, at page 3, hereinafter, "Office Action"). Applicants respectfully traverse the rejection as set forth herein.

The Examiner notes that the specification is enabling for specific hydrophobin polypeptides, HFBI and HFBII expressed in *Trichoderma* culture. Applicants have restricted the claims to these polypeptides as described in amended Claim 1 and new Claim 39. Claims 2-3 were also cancelled. All amended, cancelled and new claims are made without prejudice or disclaimer.

Therefore, in light of the amendment of Claim 1, and the addition of new Claim 39, reconsideration and withdrawal of the enablement rejection of claims 1-2, 5-9 and 32-34 are respectfully requested .

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Issues Under 35 U.S.C. § 112, Second Paragraph

Indefiniteness

Claims 1-3, 5-9 and 32-34 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants read as the invention. (See, Office Action at page 9). Applicants respectfully traverse the rejection as set forth herein.

The Examiner asserts that in Claim 1, Applicants have cited the phrase “an essential amount”; however the Examiner asserts nowhere in the claims or the specification of the application have the applicants stated, qualitatively or quantitatively, as to what is meant by “an essential amount.” Thus, the Examiner asserts that the specification does not particularly point out and distinctly claim the subject matter which the Applicants read as the invention. Applicants respectfully traverse.

It is explained in the patent application at page 16, on lines 21 to 27 (paragraph 0066 of the granted European Patent No 1204738) that:

“An essential amount means here that the host strain produces at least 50 % less amphipathic proteins, polypeptides or peptides, preferably 60-80%, most preferably 80 -100% less amphipathic proteins, polypeptides or peptides compared to the non-modified parent host strain.”

Although Applicants do not agree that the Claim 1 lacks support in the specification for “essential amount,” to expedite prosecution, Claim 1 has been amended herein, without prejudice or disclaimer, to recite, in part, “*Trichoderma* production host produces at least 50 % less HFB I or HFB II or both during cultivation, compared to the non-modified parent host strain.” Thus, at

least as amended, Claim 1 is directed to a *Trichoderma* production host that reduces the proteins HFBI or HFBII or both, during cultivation. New dependent Claims 35 and 36, which depend upon Claim 1, and independent Claim 39, have the same claim language. All amendments and new claims are made without prejudice or disclaimer.

Therefore, in light of the amendment of Claim 1, and the addition of new Claims 35, 36 and 39, reconsideration and withdrawal of the rejection of claims 1-3, 5-9 and 32-34 are respectfully requested.

Issues Under 35 U.S.C. § 103(a)

Claims 1-3, 5-9 and 32-34 stand rejected under 35 U.S.C. § 103(a) as unpatentable over WO 98/22598 in view of Nakari-Setälä et al. (Eur. J. Biochem. 248, 415-423 (1997); hereinafter “Nakari-Setälä et al.”).

Combination of the Cited References

A proper obviousness inquiry requires consideration of three factors: (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) whether or not the prior art would have taught, motivated, or suggested to those of ordinary skill in the art that they should make the claimed invention (or practice the invention in case of a claimed method or process); and (3) whether the prior art establishes that in making the claimed invention (or practicing the invention in case of a claimed method or process), there would have been a reasonable expectation of success. See M.P.E.P. § 2143.

The teaching, suggestion, motivation test is a valid test for obviousness, but one which cannot be too rigidly applied. *See KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385, 1395 (U.S. 2007). While the courts have adopted a more flexible teaching/suggestion/motivation (TSM) test in connection with the obviousness standard based on the *KSR v. Teleflex* case which involved a mechanical device in a relatively predictable technological area, it remains true that, despite this altered standard, the courts recognize inventors face additional barriers in relatively unpredictable technological areas as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) (since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish *prima facie* obviousness of new compound).

“In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification.” *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. “The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in

the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.” *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

A *prima facie* case of obviousness has not been established for this case, considering that WO 98/22598 reference concerns the culturing of *Bacillus*. Even if the cited references are combined, the cited references do not provide any teaching, suggestion, or motivation to the present invention.

The Examiner states that the reference WO 98/22598 teaches a method of reducing foam formation when cultivating a fungal production host wherein the gene encoding a protein associated with foam production has been genetically modified. According to the Examiner it would have been obvious to one of ordinary skill in the art at the time the invention was made to inactivate HFBI or HFBII by mutating their related genes for the advantages of reducing foam production in a fermentation process of the fungus *Trichoderma*. Applicants respectfully traverse.

The Applicants would like to point out that WO 98/22598 does not at all concern fungi. The reference concerns *Bacillus*, which belongs to bacteria. Since this reference is *Bacillus* specific, a person skilled in the art would not have combined the teachings of WO 98/22598 and Nakari-Setälä et al, which concerns fungi. Improvements on a *Trichoderma* based production

host processes would generally focus on applicable references dealing with fungi. Furthermore, the structure of *Bacillus* surfactin and fungal hydrophobins are totally different. The amphipathy and foam formation of surfactin is due to the fact that the surfactin molecule contains both protein and lipid parts. In fact, according to WO98/22598 (page 3 line 27) a surfactin is defined as a cyclic lipopeptide. In hydrophobins there is no lipid part. Therefore, the cited reference WO 98/22598 no longer applies.

Another distinction between the references and the present invention is that from the amino acid sequence of hydrophobins, the structure of the hydrophobin proteins could not be determined. Additionally, from the amino acid sequence of hydrophobin, it can not be concluded that hydrophobins are amphipathic. Also it was not possible to predict that hydrophobins, in particular HFBI and HFBII, express at high levels in production conditions and cause a real foam forming problems in a bioreactor. There are many possible sources of a foaming problem. In other words, the requisite reasonable expectation of success is lacking.

In the present invention, it has been shown for the first time that the reason for foaming in production conditions of a fungus can be from a protein that is not associated to lipid. This surprising finding has lead to new production host strains and to a new and inventive method with which it is possible to avoid the foaming problem during cultivation of fungal production hosts, in particular *Trichoderma*. Furthermore the claims have been amended to *Trichoderma* production hosts. These fungi produce the HFBI and HFBII proteins, which cause the foam forming problems. By these amendments the Applicants are adding further clarification of the invention, which are further reasons for patentability.

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The cited references do not suggest that the problem of foam formation could be solved by genetically modifying a *Trichoderma* production host to stop the production of the specified claimed hydrophobins.

Also, before the priority date, it was unclear whether the vegetative cells of a fungal production host could be cultivated in the presence of aeration and agitation, since the cells could be too fragile to withstand aeration and agitation within a bioreactor.

Therefore, in light of the amendment of Claim 1, the cancellation of claims 2-3 and the addition of new Claims 35, 36 and 39, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 5-9 and 32-34.

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CONCLUSION

In view of the above amendment and comments, Applicants respectfully submit that the claims are in condition for allowance. A notice to such effect is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59,228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

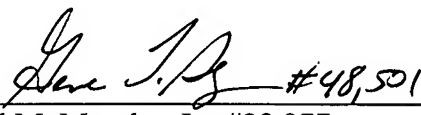
If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

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Respectfully submitted,

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